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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/053,530	01/17/2002	Jeffrey A. Ledbetter	30906/41458UTL2	8993

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/053,530	LEDBETTER ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-44,47,48,102-106 and 142-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-44, 47-48, 102-106 and 142-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-22, 45-46, 49-101 and 107-141 are cancelled.

Claims 23-25, 39, 41, 44, 47-48, 102-106 and 142 have been amended.

Claims 143-145 have been added.

2. Claims 23-44, 47-48, 102-106 and 142-145 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Withdrawn Objections/Rejections

5. The objection to the disclosure as containing embedded hyperlinks and/or other form of browser-executable code is withdrawn in view of the substitute specification filed 10/28/2003, which no longer contains the hyperlink at pg. 36, line 12.

6. The objection to the substitute specification filed 10/28/03 as not containing the updated status of USSN 07/723,454 at page 40, line 3 is withdrawn in view of the amendment to the specification filed 7/17/2006.

7. The objection to Figure 7 as not describing parts A and B is withdrawn in view of the amendment to the specification filed 7/17/2006.

8. The objection to the specification as improperly incorporating by reference the priority application 60/367,357 after the original filing of the instant application is withdrawn in view of the amendment to the specification filed 7/17/2006.

9. The objection to claims 44 and 47 as being dependent upon a cancelled claim is withdrawn in view of the amendments to the claims.

10. The rejection of claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in reciting the limitation "The protein" is withdrawn in view of the amendments to the claim.

11. The rejection of claims 39 and 142 under 35 U.S.C. 102(b) as being anticipated by Shan et al (The Journal of Immunology 162(11):6589-6595, 1999, IDS reference EA filed 7/12/02) is withdrawn in view of the amendments to the claims and applicants arguments.

12. The rejection of claim 24 under 35 U.S.C. 102(a) as being anticipated by Wu et al (Protein Engineering 14(12):1025-1033, 2001, IDS filed 6/7/04) is withdrawn in view of the amendments to the claims and applicants arguments.

Priority

Applicant argues that the priority document, USSN 60/367,358 describes a CD20 scFv fused to IgG1 hinge, CH2 and CH3 regions and also teaches "other single chain Fv-Ig molecules are within the scope of the invention and as such provides adequate written support for the present claims. This has been fully considered but is not found persuasive. The disclosure of a single specific species in prior application USSN 60/367,358 does not provide adequate written support for the myriad of other species of single chain proteins of the present claims, including those that bind to CD19, CD22, CD30 ligand, CD54, CD106, CD2, CD5, CD10, CD27, CD28, CD40, CTLA-4, 4-1BB, 4-

1BB ligand, IFN-gamma, IL-4, Il-12, IL-17, IL-17 receptor, CD59, CD48, CD72, CD70, CD86/B7.2, CD40 ligand, CD43, CD83, DEC-205, VLA-4, HER1, HER2, HER3, HER4, EGFR, VEGF, VEGFR, IGF-I, IGF-II, transferrin receptor, estrogen receptor, progesterone receptor, follicle stimulating hormone receptor, rectinoic acid receptor, MUC-1, NY-ESO-1, NA 17-A, Melan-A/MART-1, tyrosinase, Gp-100, MAGE, BAGE, GAGE, CTA class receptors, the HOM-MEL-40 antigen encoded by the SSX2 gene, CEA and PyLT. Further, the present claims are drawn to any IgG or an IgA hinge peptide where the priority application uses an IgG1 hinge and there is no disclosure in the priority document wherein the hinge peptide is an IgG or IgA in which the number of cysteine residues is reduced to one and wherein the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or substituted. Thus, not even the presently claimed CD20 single chain proteins are adequately disclosed in a manner consistent with the first paragraph of 35 U.S.C 112. Again, prior application USSN 60/367,358 discloses the anti-CD20 2H7 scFv fused to human IgG1 hinge-CH2-CH3 as well as 2H7 scFv fused with CD154, which does not provide adequate written support the broader claims of the present application as discussed supra. Therefore, the effective filing date of the presently claimed subject matter is deemed to be that of the instant application, i.e., 1/17/2002. If applicant desires priority prior to 1/17/2002; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

13. The rejection of claims 23-26, 31-33 and applied to newly added claims 143-145 are rejected under 35 U.S.C. 102(e) as being anticipated by Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04) is maintained.

The response filed 7/17/2006 has been fully considered but is not found persuasive. As discussed above Gillies et al is properly available as prior art against the pending claims, as the pending claims are not adequately supported in prior application USSN 60/367,358, filed 1/17/2001.

Applicant argues that Gillies teaches that the hinge region preferably has two cysteine residues rather than the three cysteine residues found in wild-type IgG1 hinges and according to Gillies the cysteine in the hinge that is changed to another amino acid is the first cysteine in the hinge and the remaining two cysteines are not changed. Applicant also argues the rationale behind the Gillies hinge mutations is different from that of the present invention and the constructs benefit from having Fc regions that minimize or eliminate effector functions such as ADCC, whereas the present invention is directed to single chain proteins which exhibit ADCC and/or CDC. Applicants' arguments have been fully considered but are not found persuasive. As pointed out by applicant wild-type IgG1 hinges contain three cysteines and as such the exclusionary proviso that "when the hinge contains two cysteines the first cysteine of the hinge...is not deleted or substituted" recited in claim 23 does not apply. Thus, the teachings of Gillies et al wherein the hinge peptide is an IgG1 and wherein the first hinge cysteine that normally bonds to the light chain is mutated to serine still reads on claim 23 since

such a hinge peptide is an IgG hinge peptide in which the number of cysteine residues is reduced to two (reads on newly added claims 143-145) (Gillies paragraphs [0099] and [0101]). Further, Gillies et al teach the mutation of one or more of the cysteines involved in heavy chain homodimerization, which can lead to an improvement in expression or assembly of the Ig fusion protein (see paragraph [0100]) and Gillies teaches using IgG and IgA hinges. Thus, as required by claim, 24 the mutated IgG1 hinge region of Gillies is an IgG hinge region in which the number of cysteine residues has been reduced to one by mutation with conservative amino acids or is serine (reads on newly added claims 143-145). Further, while Gillies et al does teach Ig fusions that have reduced ADCC and enhanced serum half-life, Gillies et al also teach Ig fusions that result in an increased immune response against malignancies achieved by induction of *in vitro* killing of tumor cells via ADCC and the complement system, which are merely intrinsic properties of the CH2 domain of an IgG as evidenced by Gillies at paragraph [0131]. Regarding the rationale of the Gillies teachings, a reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. The question whether a reference "teaches away" from the invention is inapplicable to an anticipation analysis. Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998).

Thus, the rejection of claims 23-26, 31-33 and applied to newly added claims 143-145 under 35 U.S.C. 102(e) as being anticipated by Gillies et al is maintained.

14. The rejection of claims 23, 25-28, 31-34, 39, 142 and applied to newly added claims 143-145 are rejected under 35 U.S.C. 102(a) as being anticipated by Wu et al (Protein Engineering 14(12):1025-1033, 2001, IDS filed 6/7/04) is maintained.

The response filed 7/17/2006 argues that claim 23 is directed to a single chain polypeptide wherein the first hinge cysteine residue is specifically not substituted when the hinge contains two cysteine residues. This has been fully considered but is not found persuasive. Since the IgG1 hinge of Wu et al contains three hinge cysteines, the exclusionary proviso that "when the hinge contains two cysteines the first cysteine of the hinge...is not deleted or substituted" does not apply and the art still reads on the claims which require an IgG hinge peptide in which the number of cysteine residues is reduced to two as taught by Wu et al. Claims 143-145 are included in the present rejection because as stated in the previous Office Action, Wu et al teach that the upper hinge cysteine is mutated to serine, which reads on claims 143-145.

Thus, the rejection of claims 23, 25-28, 31-34, 39, 142 and applied to newly added claims 143-145 are rejected under 35 U.S.C. 102(a) as being anticipated by Wu et al is maintained.

15. The rejection of claims 27-28, 34, 40-41, 44, 47, 102-103 under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04) in view of Shan et al (The Journal of immunology, 162:6589-6595, 1999, IDS reference

EA filed 7/12/02) and Liu et al (The Journal of Immunology, 139(10):3521-3526, 1987, IDS filed 6/7/04) is maintained.

The response filed 7/17/2006 has been fully considered but is not found persuasive. Applicant argues that none of the cited references disclose the hinge regions recited in either claims 23 or 24, nor do the references predict that such a singe chain protein would retain ADCC and/or CDC function. As discussed above, Gillies et al teach the hinge regions readable upon claims 23 and 24 (see item no. 13 above). Regarding the retention of ADCC and/or CDC function, Shan et al teach that the human IgG1 tail used in the scFv-Ig construct can bind Fc receptors, and this apoptotic effect may be augmented in vivo by cross-linking mediated by FcR-bearing accessory cells. Further, ADCC is an intrinsic property of the CH2 domain of IgG1 as evidenced by Gillies at paragraph [0131]. Applicant is reminded that Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced from the references and the rejection is maintained.

16. The rejection of claims 30, 35-36 and 38 under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US

2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04) in view of Kucherlapati et al (US Patent 6,150,584, filed 10/2/96) and Gilliand et al (Tissue Antigens, 47:1-20, 1996, IDS filed 6/7/04) is maintained.

The response filed 7/17/2006 has been fully considered but is not found persuasive. Applicant argues that none of the cited references disclose or suggest the hinge regions according to the present claims, nor do the references predict that such a singe chain protein would retain ADCC and/or CDC function. As discussed above, Gillies et al teach the hinge regions readable upon claims 23 and 24 (see item no. 13 above). Regarding the retention of ADCC and/or CDC function, ADCC is an intrinsic property of the CH2 domain of IgG1 as evidenced by Gillies at paragraph [0131]. Applicant is reminded that Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced from the references and the rejection is maintained.

17. The rejection of claims 48 and 104-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04)

in view of Fell et al (The Journal of Biological Chemistry, 267(22):15552-15558, 1992) and Gilliand et al (Tissue Antigens, 47:1-20, 1996, IDS filed 6/7/04) is maintained.

The response filed 7/17/2006 has been fully considered but is not found persuasive. Applicant argues that none of the cited references disclose or suggest the hinge regions according to the present claims, nor do the references predict that such a singe chain protein would retain ADCC and/or CDC function. As discussed above, Gillies et al teach the hinge regions readable upon claims 23 and 24 (see item no. 13 above). Regarding the retention of ADCC and/or CDC function, ADCC is an intrinsic property of the CH2 domain of IgG1 as evidenced by Gillies at paragraph [0131]. Applicant is reminded that Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced from the references and the rejection is maintained.

New Grounds of Objections/Rejections

18. The disclosure is objected to because of the following informalities:

a. The use of the trademark RITUXIMAB™ has been noted in this application (see pg. 9, lines 19, 22-23, 26 and 28. It should be capitalized wherever it appears and

be accompanied by the generic terminology. Applicants' cooperation is requested in reviewing the entire disclosure for additional trademarks that require correction.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

b. The specification at pg. 51, line 24 contains the term "protei" which should be corrected to "protein". The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

19. Claims 35-36 and 38 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. Claims 35-36 and 38 recite various target biological molecules some of which are expressed on the surface of a cell and some of which are not expressed on the surface of a cell, i.e., IFN-γ, 4-1BB ligand, IL-4, IL-17, CD40, VEGF, ect. Base claim 25 from which claims 35-36 and 38 depend recites that the target biological molecule is on the surface of a target cell, and thus, dependent claims 35-36 and 38 drawn to target biological molecules not on the surface of a target cell do not contain all of the limitations of the base claim and as such

do not further limit the subject matter of previous claim 25 as presently amended. Any claim which is in dependent form but which is so worded that it, in fact is not, as, for example, it does not include every limitation of the claim on which it depends, will be required to be canceled as not being a proper dependent claim; and cancellation of any further claim depending on such a dependent claim will be similarly required.

20. Claims 23, 25-44, 47-48, 102-106 and 142-145 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 39-44, 47-48 and 142 are indefinite in the recitation "wherein said binding domain polypeptide is a single chain Fv capable of binding CD20" in claim 39. Base claim 23 from which the claims depend recites that "the first cysteine of the hinge region that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or substituted". As evidenced by Shan et al (The Journal of immunology, 162:6589-6595, 1999, IDS reference EA filed 7/12/02), a single chain Fv is defined in the art to only comprise the heavy and light chain variable regions joined by a short peptide linker, however, given that the first cysteine of the IgG or IgA hinge is not deleted or substituted, is the light chain constant region part of the single chain Fv, does the free cysteine form an interchain or intrachain disulfide bond, is the structure of the single chain Fv altered, is the single chain Fv a Fab, and does the single chain Fv remain functional in the presence of the cysteine? It is unclear what is contemplated by the presence of the first cysteine in the hinge region

when the binding domain polypeptide is a single chain Fv, which lacks the light chain constant region that typically forms a disulfide bond with the first cysteine in the hinge region. As written one of skill in the art would not be reasonably apprised of the metes and bounds of the claims.

b. Claims 23, 25-44, 47-48, 102-106 and 142-145 are indefinite in the recitation "wherein said hinge peptide is an IgG or IgA hinge peptide in which the number of cysteine residues is reduced to two, provided that when the hinge peptide contains two cysteines the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or substituted..." as it is unclear what is contemplated by the phrase. Are the hinge regions reduced to two cysteines wherein the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region is not deleted or substituted? If the hinge peptide does not contain two cysteines as in the case of IgG and IgA hinge peptides is the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region is deleted or substituted?

Conclusion

21. No claim is allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER